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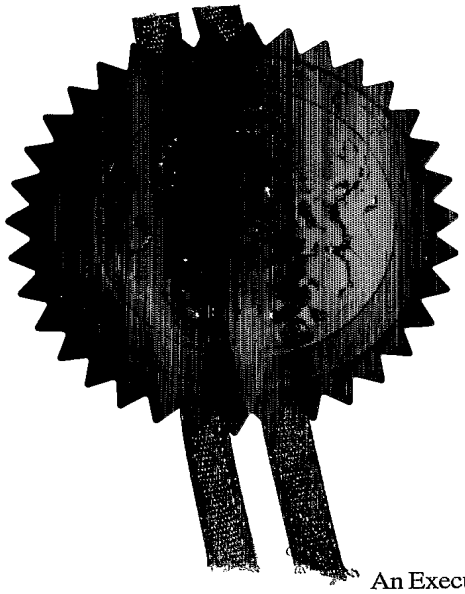

Signed Stephen Hordley

Dated 18 March 2005

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1.	Your reference	47627.GB03/NT
2.	Patent application number *(The Patent Office will fill in this part)*	0413627.1 18 JUN 2004
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	Cambridge Biotechnology Limited P.O. Box 230 Cambridge CB2 1XJ United Kingdom
	Patents ADP number *(if you know it)*	8208761002
	If the applicant is a corporate body, give the country/state of incorporation	United Kingdom
4.	Title of the invention	Analgesics
5.	Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent	Reddie & Grose 16 Theobalds Road LONDON WC1X 8PL
	Patents ADP number *(if you know it)*	91001 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
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Yes

Patents Form 1/77

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Continuation sheets of this form	0
Description	23
Claim(s)	9
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Priority documents	0
Translations of priority documents	0
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	0
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11. I/We request the grant of a patent on the basis of this application.

Signature(s) Reddie & Grose Date 18 June 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr N Thornton
01223 -360 650

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Analgesics

This invention relates to analgesic compounds and to methods of preventing, treating, or ameliorating pain using these compounds.

Pain has two components, each involving activation of sensory neurons. The first component is the early or immediate phase when a sensory neuron is stimulated, for instance as the result of heat or pressure on the skin. The second component is the consequence of an increased sensitivity of the sensory mechanisms innervating tissue which has been previously damaged. This second component is referred to as hyperlagesia, and is involved in all forms of chronic pain arising from tissue damage, but not in the early or immediate phase of pain perception.

Thus, hyperalgesia is a condition of heightened pain perception caused by tissue damage. This condition is a natural response of the nervous system apparently designed to encourage protection of the damaged tissue by an injured individual, to give time for tissue repair to occur. There are two known underlying causes of this condition, an increase in sensory neuron activity, and a change in neuronal processing of nociceptive information which occurs in the spinal cord. Hyperalgesia can be debilitating in conditions of chronic inflammation (e.g. rheumatoid arthritis), and when sensory nerve damage has occurred (i.e. neuropathic pain).

Two major classes of analgesics are known: (i) non steroidal anti-inflammatory drugs (NSAIDs) and the related COX-2 inhibitors; and (ii) opiates based on morphine. Analgesics of both classes are effective in controlling normal, immediate or nociceptive pain. However, they are less effective against some types of hyperalgesic pain, such as neuropathic pain. Many medical practitioners are reluctant to prescribe opiates at the high doses required to affect neuropathic pain because of the side effects caused by administration of these compounds (such as restlessness, nausea, and vomiting), and the possibility that patients may become addicted to them. NSAIDs are much less potent than opiates, so even higher doses of these compounds are required.

However, this is undesirable because these compounds cause irritation of the gastro-intestinal tract.

Adenosine A1 receptor agonists are known to act as powerful analgesics (Sawynok, Eur J Pharmacol. (1998) 347, 1-11), and adenosine A2A receptor agonists are known to act as anti-inflammatory agents. However, development of adenosine-based therapies has generally been precluded because they have unacceptable side effects. Selective A1 receptor agonists cause bradycardia, and A2A receptor agonists cause widespread vasodilation with consequent hypotension and tachycardia.

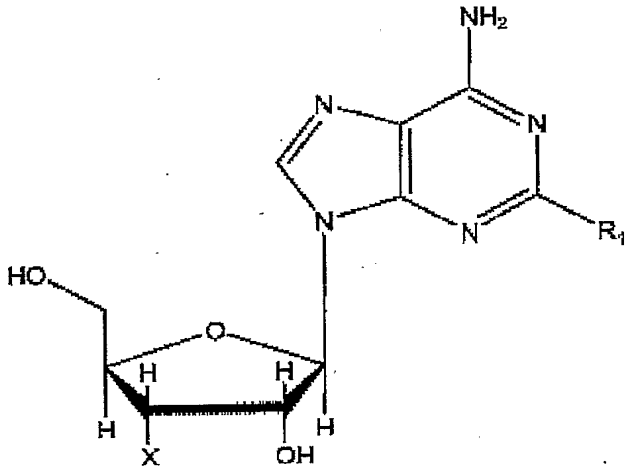
There is, therefore, a need to provide analgesics, particularly anti-hyperalgesics, which are sufficiently potent to control pain perception in neuropathic and other hyperalgesic syndromes, and which do not have serious side effects or cause patients to become addicted to them.

Spongosine was first isolated from the tropical marine sponge, *Cryptotethia crypta* in 1945 (Bergmann and Feeney, J. Org. Chem. (1951) 16, 981, Ibid (1956) 21, 226), and was the first methoxypurine found in nature. It is also known as 2-methoxyadenosine, or 9H-purin-6-amine, 9-α-D-arabinofuranosyl-2-methoxy. The first biological activities of spongosine were described by Bartlett *et al.* (J. Med. Chem. (1981) 24, 947-954) who disclosed that this compound has muscle relaxant, hypothermic, hypotensive, and anti-inflammatory activity (anti-inflammatory activity was determined using the rat paw edema model) in rats.

The affinity of spongosine for the rat adenosine A1 and A2A receptors has been determined. The Kd values obtained (in the rat) were 340nM for the A1 receptor and 1.4μM for the A2A receptor, while the EC50 value for stimulation of the rat A2A receptor was shown to be 3μM (Daly *et al.*, Pharmacol. (1993) 46, 91-100). In the guinea pig, the efficacy of spongosine was tested in the isolated heart preparation and the EC50 values obtained were 10 μM and 0.7 μM for the adenosine A1 and A2A receptors, respectively (Ueeda et al J Med Chem (1991) 34, 1334-1339). Because of the low potency and poor receptor selectivity of this compound it was largely ignored in favour of more potent and receptor selective adenosine receptor agonists.

It has surprisingly been found that spongosine is an effective analgesic at doses as much as one hundred times lower than would be expected to be required based on the known affinity of this compound for adenosine receptors. At these doses, spongosine does not cause the significant side effects associated with higher doses of this compound, or other adenosine receptor agonists. The activity of spongosine and related compounds as analgesics is the subject of International patent application nos. PCT/GB03/05379 and PCT/GB04/00935 (unpublished at the filing date of the present application).

According to the invention there is provided adenosine receptor agonists of the following formulae:

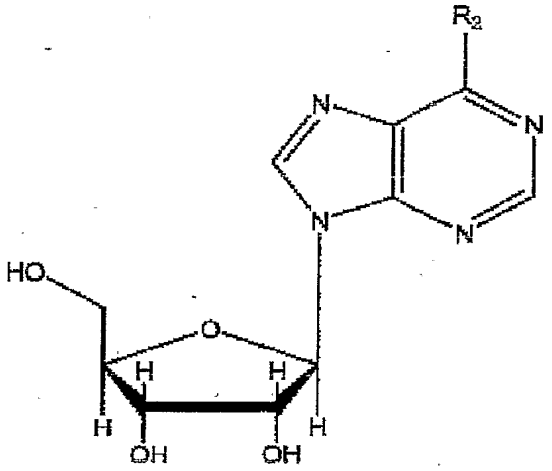


(I)

wherein:

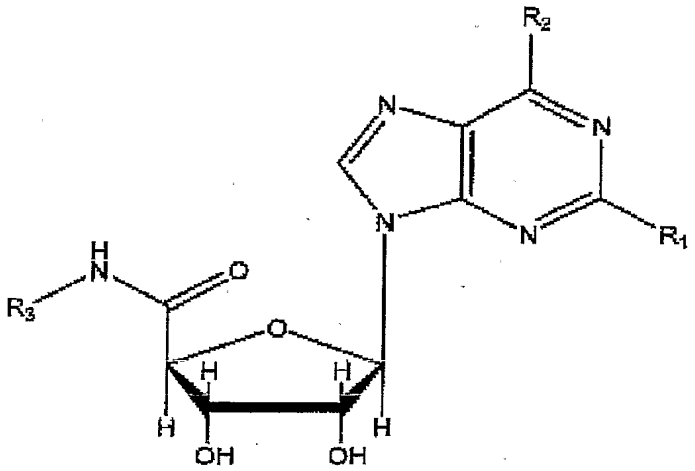
when X = OH, R_1 is C_1 or C_4-C_6 alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1, C_2, C_5, or C_6 alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or OCH_2CH_2OH; or

when X = H, R_1 is *n*-hexyloxy;



(II)

wherein R_2 is NMe_2, N-(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



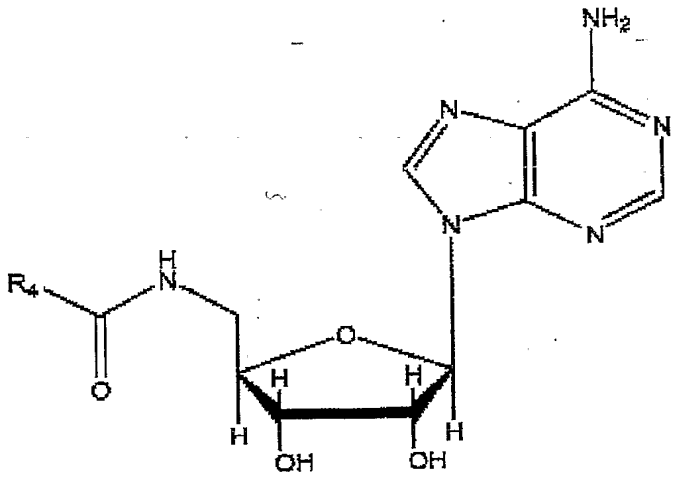
(III)

wherein:

when R_1 = H, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group (NHMe); or

when R_1 = H, R_3 is H, and R_2 is NH_2; or

when R_1 is OMe, R_3 is Ph, and R_2 is NH_2;



(IV)

wherein R_4 is *n*-propyl or $NHCH_2CH_3$;

or a pharmaceutically acceptable salt thereof.

It is believed that compounds of formulae (I)-(IV) have analgesic activity and can be administered with reduced probability and severity of side effects compared to other adenosine receptor agonists.

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, particularly hyperalgesia.

There is also provided according to the invention a method of preventing, treating, or ameliorating pain (particularly hyperalgesia) which comprises administering a compound of formula (I), (II), (III), or (IV) to a subject in need of such prevention, treatment, or amelioration.

Preferred compounds of formula (I), (II), (III), and (IV) are detailed in the Examples.

Compounds of formulae (I)-(IV) are believed to be effective in inhibiting pain perception in mammals suffering from pain, in particular neuropathic or inflammatory

pain, even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. Therefore, it is believed that compounds of formulae (I)-(IV) can treat pain (particularly neuropathic and inflammatory pain) without causing the significant side effects associated with administration of other adenosine receptor agonists.

As mentioned above hyperalgesia is a consequence in most instances of tissue damage, either damage directly to a sensory nerve, or damage of the tissue innervated by a given sensory nerve. Consequently, there are many conditions in which pain perception includes a component of hyperalgesia.

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of neuropathy, including Diabetic Neuropathy, Polyneuropathy, Cancer Pain, Fibromyalgia, Myofascial Pain Syndrome, Osteoarthritis, Pancreatic Pain, Pelvic/Perineal pain, Post Herpetic Neuralgia, Rheumatoid Arthritis, Sciatica/Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, HIV pain, Trigeminal Neuralgia, Chronic Neuropathic Pain, Lower Back Pain, Failed Back Surgery pain, back pain, post-operative pain, post physical trauma pain (including gunshot, road traffic accident, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel Pain, Phantom Limb Pain, Obstetric Pain (labour/C-Section), Renal Colic, Acute Herpes Zoster Pain, Acute Pancreatitis Breakthrough Pain (Cancer), Dysmenorhoea/Endometriosis.

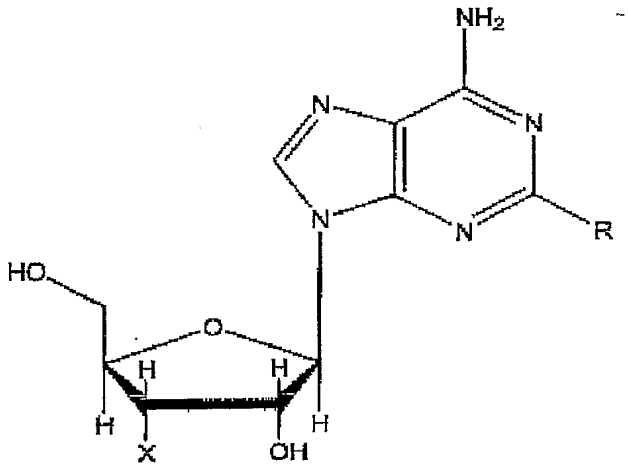
According to the invention there is also provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of inflammatory disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage, including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of

reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis, bowel pain, cancer pain, back pain, fibromyalgia, post-operative pain.

It has also been appreciated that spongosine may be effective in the prevention, treatment, or amelioration of ischaemic pain. It is believed that compounds related to spongosine may also be effective against ischaemic pain.

According to the invention there is provided use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, in particular ischaemic pain:

(V)



wherein R is C_{1-4} alkoxy, and X is H or OH,

or a pharmaceutically acceptable salt thereof.

Preferably R is C_{1-4} alkoxy, and X is OH, or a pharmaceutically acceptable salt thereof.

There is also provided according to the invention a method of preventing, treating, or ameliorating ischaemic pain, which comprises administering a compound of formula (V) to a subject in need of such prevention, treatment, or amelioration.

It has also been appreciated that compounds of formula (I)-(IV) may be effective in the prevention, treatment, or amelioration of ischaemic pain.

The term "ischaemic pain" is used herein to mean pain associated with a reduction in blood supply to a part of the body. A reduced blood supply limits the supply of oxygen (hypoxia) and energy to that part of the body. Ischaemia arises from poor blood perfusion of tissues and so ischaemic pain arises in coronary artery disease, peripheral artery disease, and conditions which are characterized by insufficient blood flow, usually secondary to atherosclerosis. Other vascular disorders can also result in ischaemic pain. These include: left ventricular hypertrophy, coronary artery disease, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis oblitterens), arteritis, diastolic dysfunction and systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (both Types I and II), thromboembolisms. Haemorrhagic accidents can also result in ischaemic pain. In addition poor perfusion can result in neuropathic and inflammatory pain arising from hypoxia-induced nerve cell damage (e.g. in cardiac arrest or bypass operation, diabetes or neonatal distress).

It has also been appreciated that compounds of formulae (I)-(V) may be effective in preventing, treating, or ameliorating macro and micro vascular complications of type 1 or 2 diabetes (including retinopathy, nephropathy, autonomic neuropathy), or blood vessel damage caused by ischaemia (either diabetic or otherwise) or atherosclerosis (either diabetic or otherwise).

According to the invention, there is provided use of a compound of formula (I), (II), (III), (IV), or (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of macro or micro vascular complications of type 1 or 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis.

According to the invention there is also provided a method of preventing, treating, or ameliorating macro or micro vascular complications of type 1 or 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis, in a subject in need of such prevention, treatment, or amelioration, which comprises administering a compound of formula (I), (II), (III), (IV), or (V) to the subject.

Preferred compounds of formula (V) are 2-methoxyadenosine, 2-ethoxyadenosine, and 2-butyloxyadenosine.

Compounds of formulae (I)-(V) are believed to be effective in prevention, treatment, or amelioration of ischaemic pain (or macro or micro vascular complications of type 1 and 2 diabetes, including retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis (either diabetic or otherwise)) even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. At these doses, it is believed that the compounds do not cause the significant side effects associated with administration of higher doses of spongosine, or other adenosine receptor agonists.

The amount of a compound of formula (I)-(V) that is administered to a subject is preferably an amount which gives rise to a peak plasma concentration that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

It will be appreciated that the EC50 value of the compound is likely to be different for different adenosine receptors (i.e. the A1, A2A, A2B, A3 adenosine receptors). The amount of the compound that is to be administered should be calculated relative to the lowest EC50 value of the compound at the different receptors.

Thus, preferably the amount of a compound of the invention that is administered to a subject should be an amount which gives rise to a peak plasma concentration that is less than the lowest EC50 value of the compound at adenosine receptors.

Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value.

Preferably the amount of a compound of the invention that is administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value of the compound at adenosine receptors.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour between one thousandth and one fifth, or one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the EC50 value of the compound at adenosine receptors at pH 7.4.

For the avoidance of doubt, the EC50 value of a compound is defined herein as the concentration of the compound that provokes a receptor response halfway between the baseline receptor response and the maximum receptor response (as determined, for example, using a dose-response curve).

The EC50 value should be determined under standard conditions (balanced salt solutions buffered to pH 7.4). For EC50 determinations using isolated membranes, cells and tissues this would be in buffered salt solution at pH 7.4 (e.g. cell culture

medium), for example as in Daly *et al.*, Pharmacol. (1993) 46, 91-100), or preferably as in Tilburg *et al* (J. Med. Chem. (2002) *45*, 91-100). The EC50 could also be determined *in vivo* by measuring adenosine receptor mediated responses in a normal healthy animal, or even in a tissue perfused under normal conditions (i.e. oxygenated blood, or oxygenated isotonic media, also buffered at pH 7.4) in a normal healthy animal.

Alternatively, the amount of a compound of the invention that is administered may be an amount that results in a peak plasma concentration that is less than the lowest or highest Kd value of the compound at adenosine receptors (i.e. less than the lowest or highest Kd value of the compound at A1, A2A, A2B, and A3 adenosine receptors). Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one third, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest or highest Kd value.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for at least one hour between one thousandth and one fifth, more preferably between one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the Kd value of the compound at adenosine receptors.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one fiftieth to one third, or one tenth to one fifth) of the lowest or highest Kd value of the compound at adenosine receptors.

The Kd value of the compound at each receptor should be determined under standard conditions using plasma membranes as a source of the adenosine receptors derived either from tissues or cells endogenously expressing these receptors or from cells transfected with DNA vectors encoding the adenosine receptor genes. Alternatively whole cell preparations using cells expressing adenosine receptors can be used. Labelled ligands (e.g. radiolabelled) selective for the different receptors should be used in buffered (pH7.4) salt solutions (see e.g. Tilburg et al, J. Med. Chem. (2002) 45, 420-429) to determine the binding affinity and thus the Kd of the compound at each receptor.

Alternatively, the amount of a compound of the invention that is administered may be an amount that is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount (or dose) of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount of the compound that gives rise to the side effects.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth of the minimum dose that gives rise to the side effects.

Alternatively, the amount of a compound of the invention that is administered may be an amount that gives rise to plasma concentrations that are one ten thousandth to one

fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that cause bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that causes the side effects.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth, of the minimum plasma concentration that causes the side effects.

It is expected that the amount of a compound of the invention that is administered should be 0.001-15 mg/kg. The amount may be less than 6 mg/kg. The amount may be at least 0.001, 0.01, or 0.1 mg/kg. The amount may be less than 0.1, or 0.01 mg/kg. Preferred ranges are 0.001-10, 0.001-5, 0.001-2, 0.001-1, 0.001-0.1, 0.001-0.01, 0.01-15, 0.01-10, 0.01-5, 0.01-2, 0.01-1, 0.1-10, 0.1-5, 0.1-2, 0.1-1, 0.2-1.2, 0.2-1, 0.6-1.2, mg/kg.

Preferred doses for a human subject (for example a 70kg subject) are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7-70mg, or 14-70mg.

It is believed that the dosage amounts specified above are significantly lower (up to approximately 1000 times lower) than would be expected to be required for an

analgesic effect based on the EC50 value of the compound at the adenosine A2A receptor.

The dosage amounts specified above are aimed at producing plasma concentrations that are approximately one thousandth to one hundredth of the EC50 value of spongosine at the adenosine A1 receptor.

The appropriate dosage of a compound of the invention will vary with the age, sex, weight, and condition of the subject being treated, the potency of the compound, and the route of administration, etc. The appropriate dosage can readily be determined by one skilled in the art.

A compound of the invention may be administered with or without other therapeutic agents, for example analgesics or anti-inflammatories (such as opiates, steroids, NSAIDs, cannabinoids, tachykinin modulators, or bradykinin modulators) or anti-hyperalgesics (such as gabapentin, pregabalin, cannabinoids, sodium or calcium channel modulators, anti-epileptics or anti-depressants).

In general, a compound of the invention may be administered by known means, in any suitable formulation, by any suitable route. A compound of the invention is preferably administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally. Other suitable routes include intravenous, intramuscular, subcutaneous, inhaled, and topical. The amount of drug administered will typically be higher when administered orally than when administered, say, intravenously.

It will be appreciated that a compound of the invention may be administered together with a physiologically acceptable carrier, excipient, or diluent.

Suitable compositions, for example for oral administration, include solid unit dose forms, and those containing liquid, e.g. for injection, such as tablets, capsules, vials and ampoules, in which the active agent is formulated, by known means, with a physiologically acceptable excipient, diluent or carrier. Suitable diluents and carriers

are known, and include, for example, lactose and talc, together with appropriate binding agents etc.

A unit dosage of a compound of the invention typically comprises up to 500 mg (for example 1 to 500 mg, or (preferably) 5 to 500 mg) of the active agent. Preferably the active agent is in the form of a pharmaceutical composition comprising the active agent and a physiologically acceptable carrier, excipient, or diluent. The preferred dosage is 0.1 to 2, e.g. 0.5 to 1, typically about 0.2 or 0.6, mg of the active agent per kg of the (human) subject. Preferred amounts of the active agent are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7 to 70mg, or 14 to 70mg. At these levels, it is believed that effective treatment can be achieved substantially without a concomitant fall (for example, no more than 10%) in blood pressure.

Preferably a compound of the invention is administered at a frequency of 2 or 3 times per day.

Use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain, or a method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (I) in accordance with the invention may exclude prevention, treatment, or amelioration of pain resulting from damage caused to organs as a consequence of reperfusion following an ischaemic episode, for example a myocardial infarct, or a stroke.

Use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain in accordance with the invention may exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

A method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (V) in accordance with the invention may

exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

Embodiments of the invention are described in the following examples with reference to the accompanying drawings in which:

Figure 1 shows the effect of spongosine (0.6 mg/kg p.o.) on A: blood pressure in normal rats; B: heart rate;

Figure 2 shows the change in plasma concentration over time after administration of spongosine

Figure 3 shows the anti-hyperalgesic actions of spongosine (0.6 mg/kg p.o.) on carrageenan induced hyperalgesia. A: time course (*$p<0.05$, **$p<0.01$ versus vehicle (Sidak's), $p>0.05$ versus BL over 5 hrs for Spongosine and IND (Dunnett's)); B: dose dependency of the anti-hyperalgesic effect;

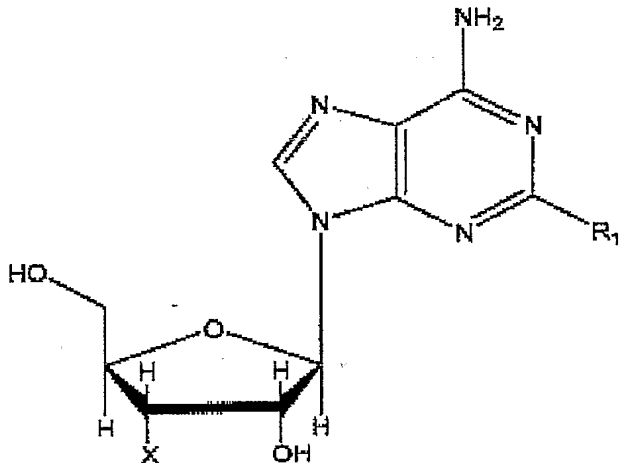
Figure 4 shows the anti-hyperalgesic actions of spongosine (0.6 mg/kg p.o.) in the chronic constriction injury model of neuropathic pain (*$p<0.05$, **$p<0.01$ vs veh (ANOVA Sidak's);

Figure 5 shows the effect of spongosine (0.6 mg/kg p.o.) in the presence and absence of naloxone in the chronic constriction injury model of neuropathic pain; and

Figure 6 shows the additive effect of spongosine and gabapentin in the chronic constriction injury model of neuropathic pain.

Structures of preferred compounds of the invention are given in the Examples below. A Ki value is given for each compound. To calculate this, rat striatal membranes were incubated for 90 minutes at 22°C in the presence of 2nM [3H]-CGS21680, 1Unit/ml adenosine deaminase and increasing concentrations of the compound being studied, prior to filtration and liquid scintillation counting.

Example 1



When X = OH

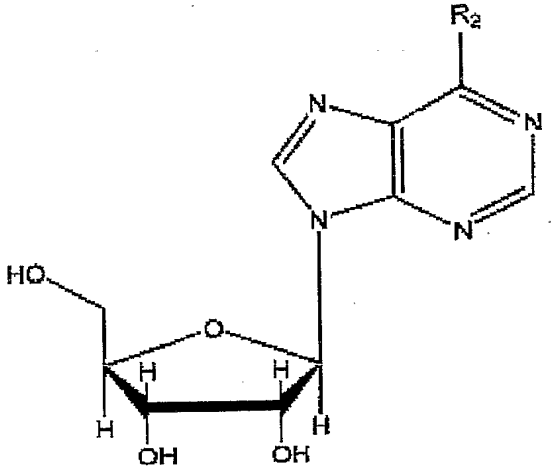
Compound No.	Structure R_1	(Ki) nM
1	OCH3	1300
2	$OCH_2CH_2CH_2CH_3$	280
3	O $CH_2CH_2CH_2CH_2CH_2CH_3$	1500
4	OPh	2500
5	O-(4-cyano)Ph	1300
6	O-(3-Ph)Ph	620
7	5-indanyloxy	760
8	O-(3-$CH(CH_3)_2$)Ph	560
9	$NH(CH_3)$	1356
10	$NHCH_2CH_3$	1200
11	$N(CH_3)_2$	13350
12	$NHCH_2CH_2CH_2CH_2CH_2CH_3$	290
13	NHPh	160
14	NH-(4-MeO)Ph	55
15	NH-(4-F)Ph	200
16	NH-cyclopentyl	420
17	NH-cyclohexyl	1000

18	N-CH_3, N-$CH_2CH_2CH(CH_3)_2$	4000
19	OCH_2cyclopentyl	200
20	$SO_2CH_2CH_3$	39000
21	OCH_2CH_2OH	203
22	$CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	800

When X = H

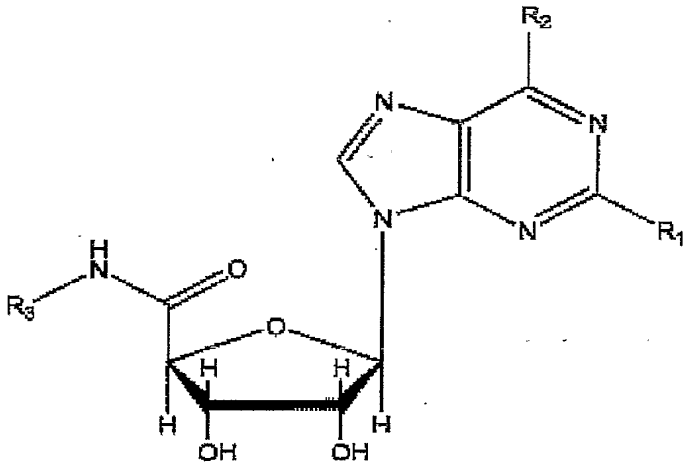
Compound No.	Structure R_1	(Ki) nM
23	O $CH_2CH_2CH_2CH_2CH_2CH_3$	2990

Example 2



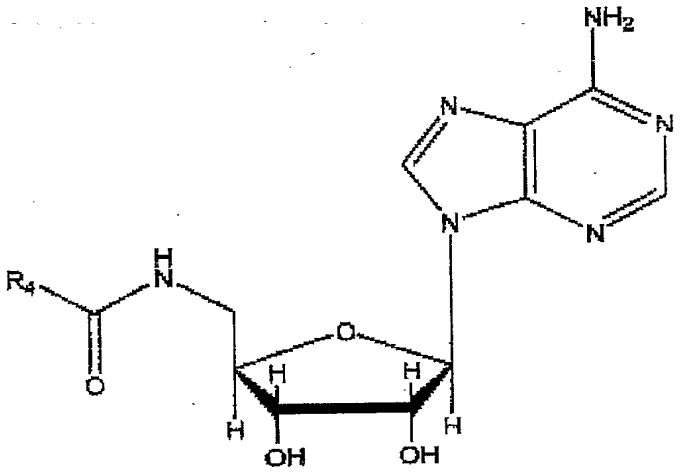
Compound No.	Structure R_2	(Ki) nM
24	$N(CH_3)_2$	450000
25	$NHCH_2CHC(CH_3)_2$	8600
26	$N\text{-}CH_3$, $N\text{-}CH_2Ph$	18500
27	Piperazinyl	5000
28	N-Me, $N\text{-}(CH_2CH_2OCH_3)$	13000

Example 3



Compound No.	R_1	R_2	R_3	(Ki) nM
29	H	NH_2	$CH(CH_3)_2$	1930
30	H	NH_2	H	270
31	H	$NHCH_3$	$CH(CH_3)_2$	2440
32	OCH_3	NH_2	Ph	26100

Example 4



Compound No.	Structure R_4	(Ki) nM
33	$CH_2CH_2CH_3$	16900
34	$NHCH_2CH_3$	6570

Example 5

Figure 1: Spongosine (0.624 mg/kg p.o.) has no significant effect on blood pressure or heart rate. An implantable radiotelemetry device was placed in the abdominal cavity of 6 rats per group. The pressure catheter of the device was inserted in the abdominal aorta and two electrodes tunnelised under the skin in a lead II position (left side of abdominal cavity/right shoulder). Individual rats were placed in their own cage on a radioreceptor (DSI) for data acquisition. A: blood pressure; B: heart rate.

Example 6

The EC50 value of spongosine at adenosine receptors (measured at pH7.4) is 900ng/ml (3 μM). Figure 2 shows the change in plasma concentration over time after administration of spongosine at 0.6 mg/kg to a rat. It can be seen that the plasma concentration remains above 2% of the EC50 value for more than 3 hours. Anti-hyperalgesic effects have been observed (without blood pressure changes) when the

peak plasma concentration is between 1% and 30% of the EC50 value determined in vitro. If the peak plasma concentration reaches the EC50 value profound reductions in blood pressure occur that last for hours.

Example 7

Figure 3: A. Spongosine (0.624mg/kg p.o.) inhibits carrageenan (CGN) induced thermal hyperalgesia (CITH) with comparable efficacy to indomethacin (3mg/kg, po). B. Concentration-response relationship for Spongosine at 3 hrs post dosing. Carrageenan (2%, 10 microlitres) was administered into the right hind paw. A heat source was placed close to the treated and untreated hind paws, and the difference in the paw withdrawal latencies is shown. Spongosine was administered at the same time as carrageenan.

Example 8

Figure 4: Spongosine (0.624mg/kg p.o.) inhibits thermal hyperalgesia caused by chronic constriction injury of the rat sciatic nerve. Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed thermal hyperalgesia in the operated leg as judged by the difference in paw withdrawal latencies of the right and left paws. Administration of spongosine reduced the hyperalgesia as shown by the reduction in the difference between the withdrawal latencies. Spongosine was as, or more, effective than carbamazepine (CBZ, 100mg/kg s.c.)

Example 9

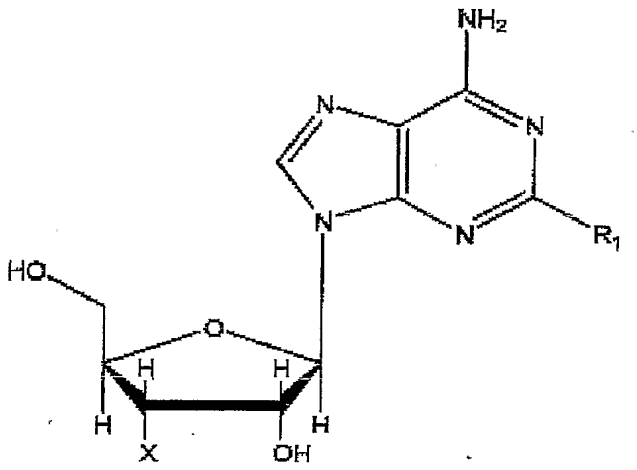
Figure 5: Spongosine (1.2 mg/kg p.o.) inhibits static allodynia caused by chronic constriction injury of the rat sciatic nerve, both in the presence and absence of naloxone (1 mg/kg s.c.). Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed static allodynia in the operated leg as judged by the difference in paw withdrawal thresholds of the right and left paws. Administration of spongosine reduced the hyperalgesia as shown by the increased paw withdrawal threshold (PWT) in the presence and absence of naloxone. Veh: vehicle.

Example 10

Figure 6: Spongosine and gabapentin inhibit static allodynia caused by chronic constriction injury of the rat sciatic nerve. Spongosine and gabapentin were administered (p.o.) in different proportions as indicated in the drawing. The total dose administered is shown on the horizontal axis, and the paw withdrawal threshold (PWT) on the vertical axis. The predicted anti-hyperalgesic effect (derived from the dose response curves obtained with each agent alone) if the effects of the two compounds are additive is shown (▪). The observed effects are indicated by (■). It is apparent that the observed effects are not significantly different from those predicted by additivity.

Claims

1. A compound of formula (I), (II), (III), or (IV):

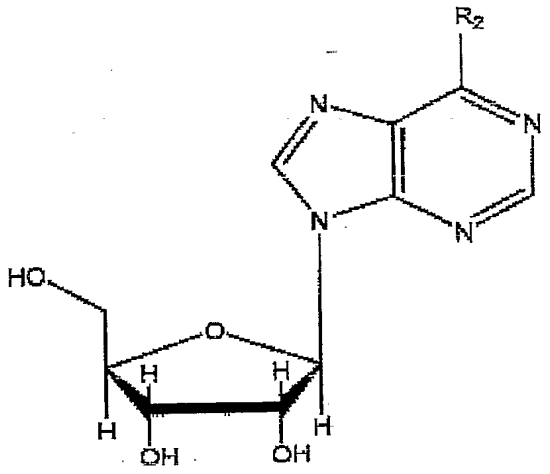


(I)

wherein:

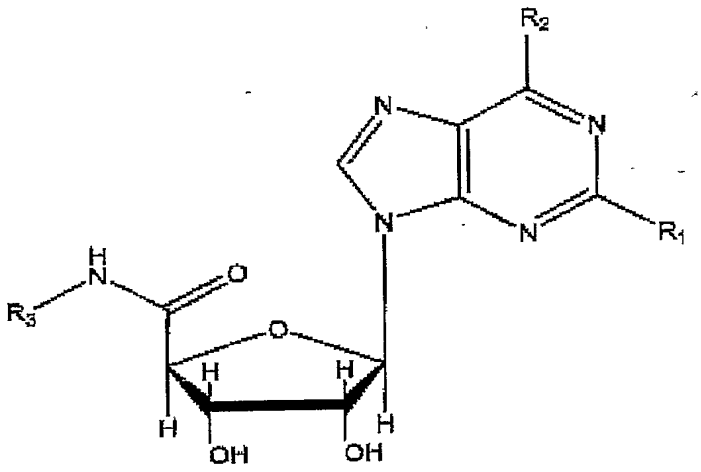
when X = OH, R_1 is C_4-C_6 alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1, C_2, C_5, or C_6 alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or OCH_2CH_2OH; or

when X = H, R_1 is *n*-hexyloxy;



(II)

wherein R_2 is NMe_2, N-(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



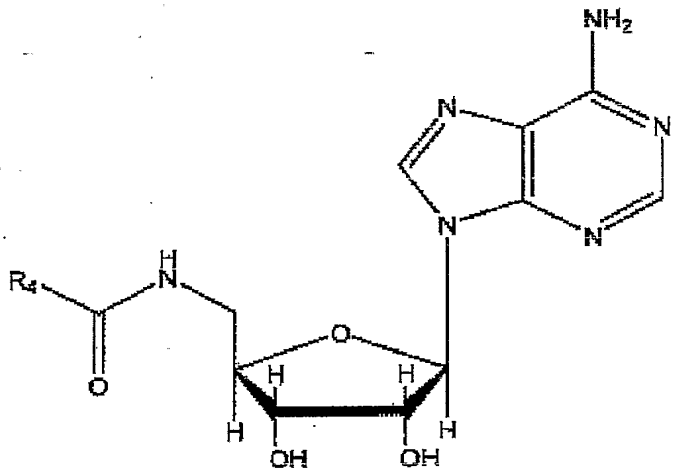
(III)

wherein:

when R_1 = H, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group (NHMe); or

when R_1 = H, R_3 is H, and R_2 is NH_2; or

when R_1 is OMe, R_3 is Ph, and R_2 is NH_2;



(IV)

wherein R_4 is *n*-propyl or $NHCH_2CH_3$;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 with a structure as defined in any of Examples 1-4.

3. A compound according to claim 1 or 2 for use as a medicament.

4. Use of a compound according to claim 1 or 2 in the manufacture of a medicament for the prevention, treatment, or amelioration of pain.

5. Use according to claim 4, wherein the pain is hyperalgesia.

6. Use according to claim 5, wherein the hyperalgesia is neuropathic pain.

7. Use according to any of claims 4 to 6 for the prevention, treatment, or amelioration of: pain associated with cancer, pancreatic pain, pelvic/perineal pain, pain associated with HIV infection, chronic neuropathic pain, lower back pain, failed back surgery pain, back pain, post-operative pain, post physical trauma pain, cardiac pain, chest pain, pelvic pain/PID, joint pain, neck pain, bowel pain, phantom limb

pain, obstetric pain, acute herpes zoster pain, acute pancreatitis breakthrough pain, or for the prevention, treatment, or amelioration of neuropathic or other pain caused by, or associated with diabetic neuropathy, polyneuropathy, fibromyalgia, myofascial pain syndrome, osteoarthritis, post herpetic neuralgia, rheumatoid arthritis, sciatica/lumbar radiculopathy, spinal stenosis, temporo-mandibular joint disorder, trigeminal neuralgia, renal colic, dysmenorhoea/endometriosis.

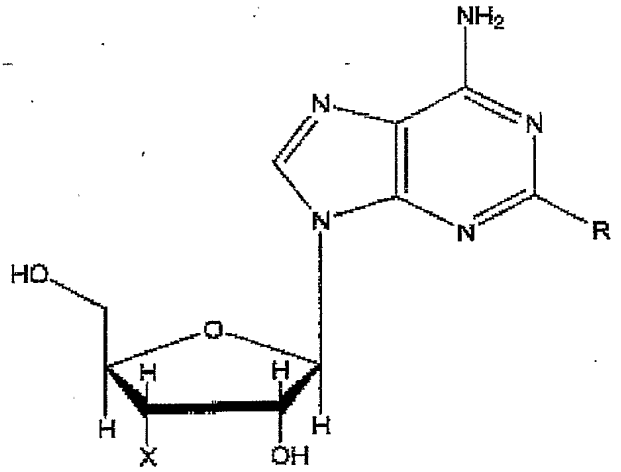
8. Use according to claim 5, wherein the hyperalgesia is inflammatory pain.

9. Use according to any of claims 4, 5, or 8 wherein the pain is caused by or associated with an inflammatory or immune disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage.

10. Use according to any of claims 4, 5, 8, or 9 for the prevention, treatment, or amelioration of bowel pain, pain associated with cancer, back pain, post-operative pain, or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, autoimmune damage, graft v. host rejection, allograft rejections, fever and myalgia due to infection, fibromyalgia, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis.

11. Use according to claim 4, or use of a compound of formula (V), in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain:

(V)



wherein R is C_{1-4} alkoxy, and X is H or OH, or a pharmaceutically acceptable salt thereof.

12. Use according to claim 4 or 11 in the manufacture of a medicament for the prevention, treatment, or amelioration of pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis obliterens), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

13. Use of a compound of claim 1 or 2, or a compound of formula (V), in the manufacture of a medicament for the prevention, treatment, or amelioration of macro or micro vascular complications of type 1 and 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis.

14. Use according to any of claims 4 to 13 at a dosage which, after administration to a subject, gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

15. Use according to any of claims 4 to 14 at a dosage that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

16. Use according to claim 15, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects.

17. Use according to any of claims 4 to 16 at a dosage which, after administration to a subject, gives rise to a plasma concentration of the compound that is maintained for more than one hour between one thousandth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

18. Use according to any of claims 4 to 17 at a dosage of less than 6mg/kg.

19. Use according to any of claims 4 to 18 at a dosage of at least 0.01mg/kg.

20. Use according to any of claims 4 to 19 at a dosage of 0.2 to 1mg/kg.

21. A method of preventing, treating, or ameliorating pain which comprises administering a compound according to claim 1 or 2 to a subject in need of such prevention, treatment, or amelioration.

22. A method of preventing, treating, or ameliorating ischaemic pain which comprises administering a compound of formula (V) to a subject in need of such prevention, treatment, or amelioration.

23. A method of preventing, treating, or ameliorating macro or micro vascular complications of type 1 and 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis which comprises administering a compound of claim 1 or 2 , or a compound of formula (V), to a subject in need of such prevention, treatment, or amelioration.

24. A method according to any of claims 21 to 23, wherein the compound is administered at a dose that gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.

25. A method according to any of claims 21 to 24, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.

26. A method according to any of claims 21 to 25, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.

27. A method according to any of claims 21 to 26, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.

28. A method according to any of claims 21 to 27, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.

29. A method according to any of claims 21 to 28, wherein the compound is administered to the subject in an amount that is one ten thousandth to one fifth of the minimum amount of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

30. A method according to any of claims 21 to 29, wherein the compound is administered at a dose that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the dose is to be administered.

31. A method according to claim 30, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects

32. A method according to any of claims 21 to 31, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the minimum plasma concentration of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

33. A method according to any of claims 21 to 32, wherein the compound is administered at a dose that results in a plasma concentration of the compound that is maintained for more than one hour between one hundredth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.

34. A method according to any of claims 21 to 33, wherein the compound is administered at a dose of less than 6mg/kg.

35. A method according to any of claims 21 to 34, wherein the compound is administered at a dosage of 0.001 to 6 mg/kg.

36. A method according to any of claims 21 to 35, wherein the compound is administered at a dose of at least 0.01mg/kg.

37. A method according to any of claims 21 to 36, wherein the compound is administered at a dose of 0.2 to 1mg/kg.

38. A method according to any of claims 21 to 37, wherein the compound is administered orally, parenterally, sublingually, transdermally, intrathecally, transmucosally, intravenously, intramuscularly, subcutaneously, topically, or by inhaling.

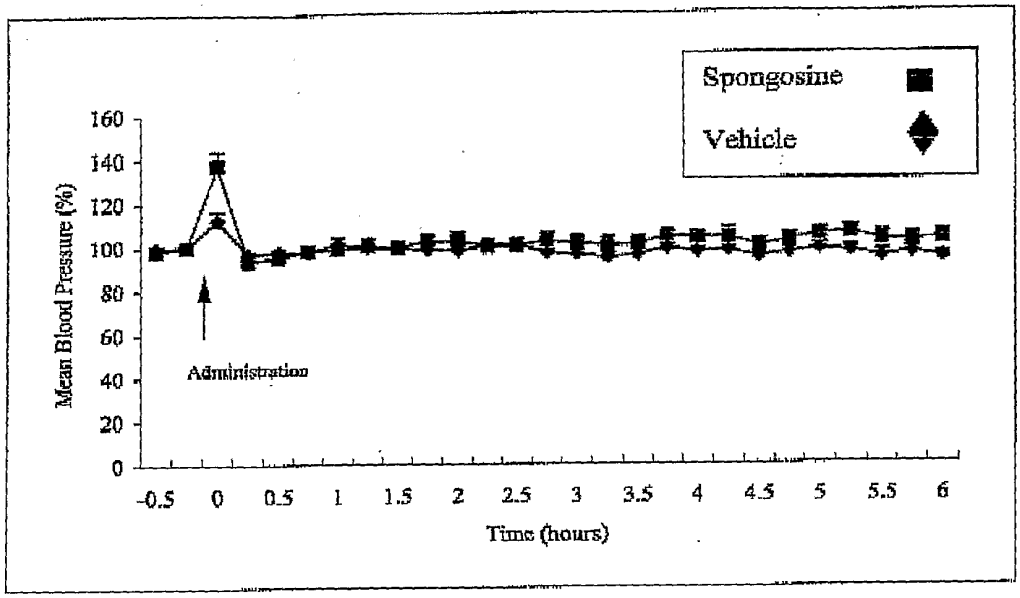
39. A method according to any of claims 21 to 38, wherein the compound is administered at a frequency of 2 or 3 times per day.

40. A method according to any of claims 21 to 39, wherein the subject is a human subject.

41. A method according to any of claims 21 to 40 for the prevention, treatment, or amelioration of ischaemic pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncopy, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis oblitterens), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

Figure 1

A)



B)

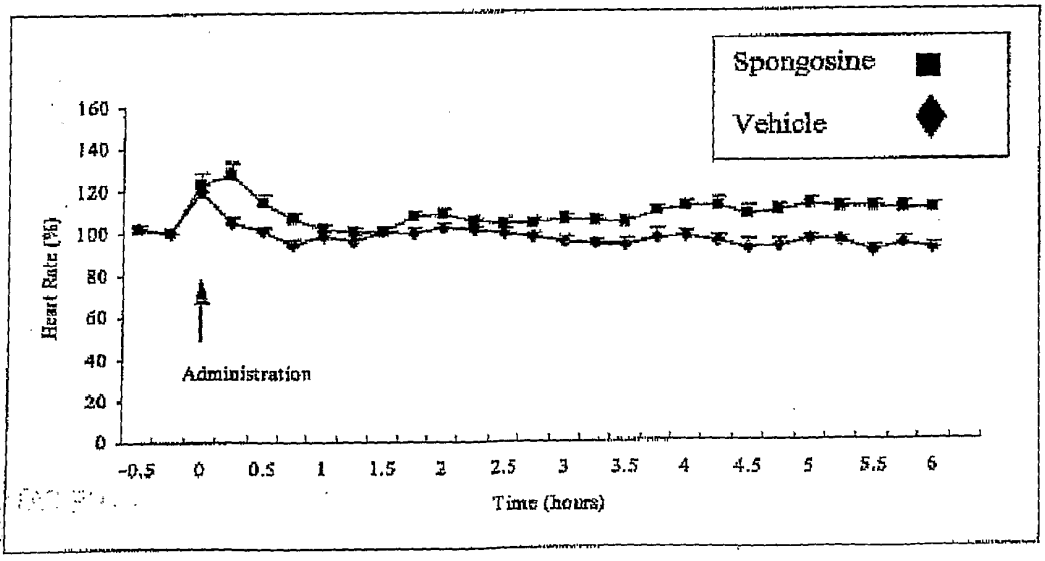


Figure 2

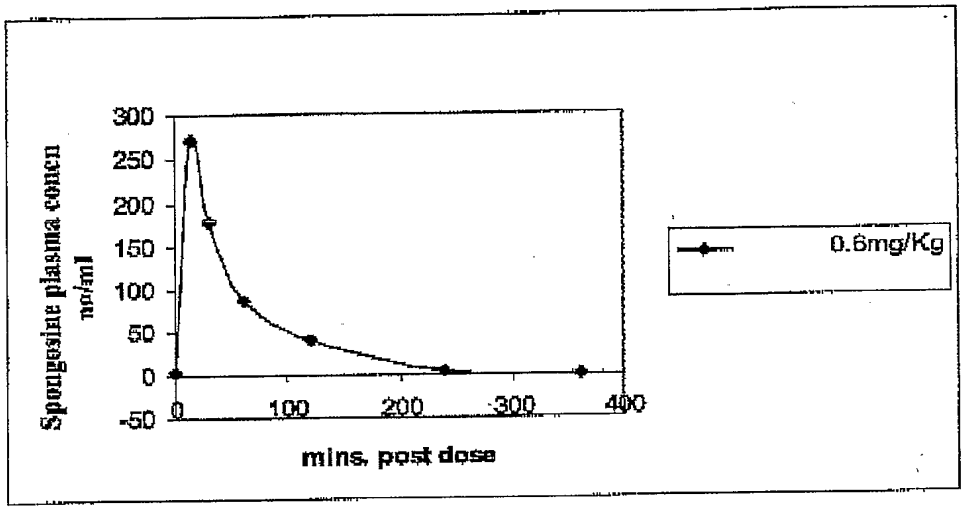
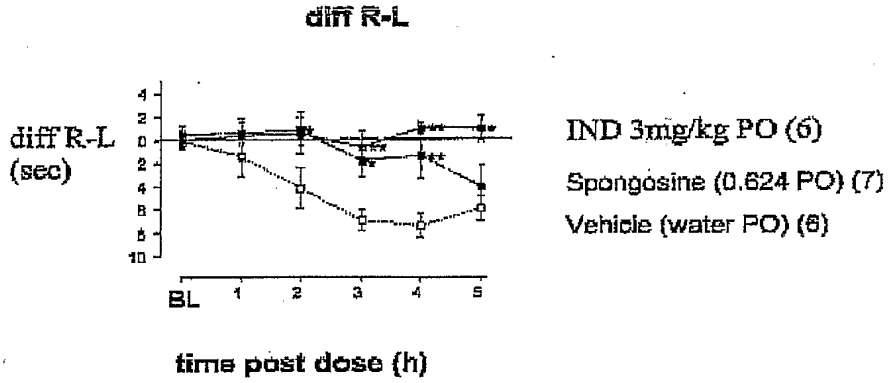

Spongosine plasma concen
ng/ml
300
250
200
150
100
50
0
-50
0
100
200
300
400
mins. post dose
0.6mg/Kg

Figure 3

A)


diff R-L
diff R-L (sec)
4
2
0
-2
-4
-6
-8
-10
BL
1
2
3
4
5
time post dose (h)
IND 3mg/kg PO (6)
Spongosine (0.624 PO) (7)
Vehicle (water PO) (6)

B)

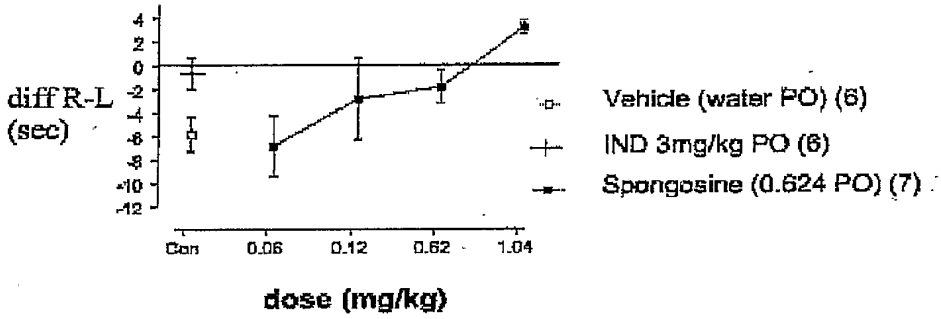

3 hrs post CGN
diff R-L (sec)
4
2
0
-2
-4
-6
-8
-10
-12
Con
0.06
0.12
0.62
1.04
dose (mg/kg)
Vehicle (water PO) (6)
IND 3mg/kg PO (6)
Spongosine (0.624 PO) (7)

Figure 4

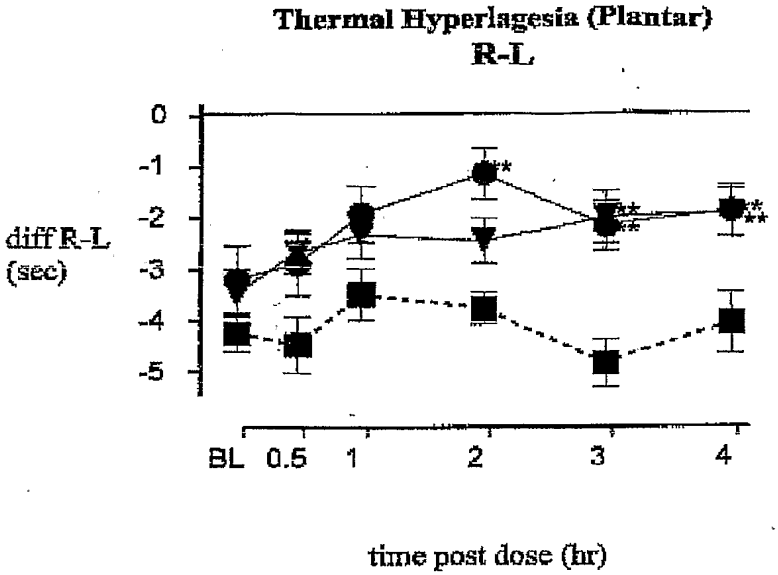
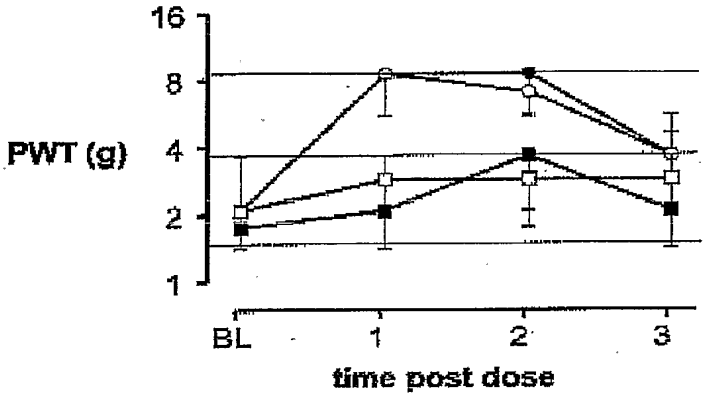

Thermal Hyperlagesia (Plantar)
R-L
diff R-L
(sec)
0
-1
-2
-3
-4
-5
BL
0.5
1
2
3
4
time post dose (hr)
Spongosine (0.624 mg/kg PO)
CBZ (100mg/kg SC)

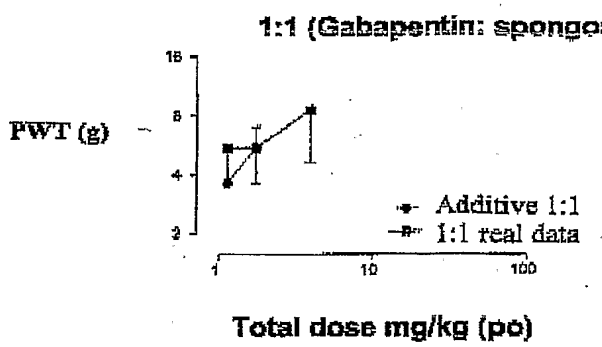
Figure 5



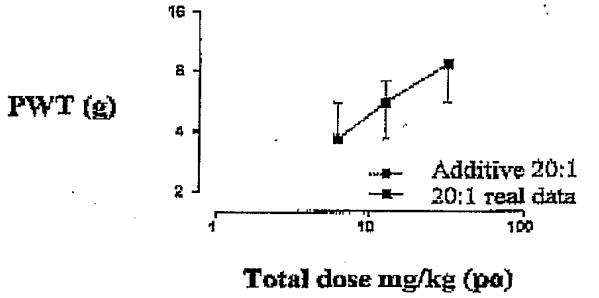
Vehicle + Vehicle
Vehicle + spongosine (1.2 p.o.)
Nalox (1 s.c.) + Vehicle
Nalox (1 s.c.) + spongosine (1.2 p.o.)

Figure 6

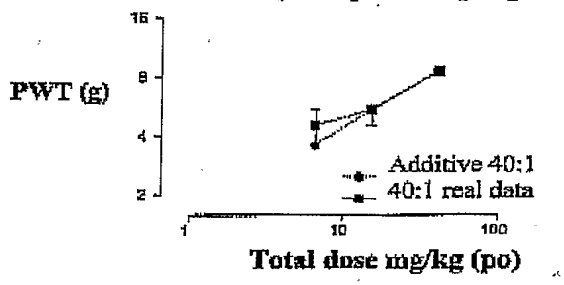
A)


1:1 (Gabapentin: spongosine)
PWT (g)
16
8
4
2
Additive 1:1
1:1 real data
1
10
100
Total dose mg/kg (po)

B)


20:1 (Gabapentin: spongosine)
PWT (g)
16
8
4
2
Additive 20:1
20:1 real data
1
10
100
Total dose mg/kg (po)

C)


40:1 (Gabapentin: spongosine)
PWT (g)
16
8
4
2
Additive 40:1
40:1 real data
1
10
100
Total dose mg/kg (po)